

Associated bone mineral density and obstructive sleep apnea in chronic obstructive pulmonary disease

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Background: Osteoporosis is an important issue for patients with chronic obstructive pulmonary disease (COPD). Worse systemic inflammation and reduced exercise capacity have been reported in COPD patients with obstructive sleep apnea (OSA), implying that OSA may be an independent factor for osteoporosis in COPD patients.

Methods: A total of 66 patients with bone mineral density (BMD) and polysomnography results from a previous COPD cohort (January 2008 to January 2013) were retrospectively enrolled. Clinical characteristics such as medication, pulmonary function, BMD, and results of polysomnography were analyzed.

Results: The BMD in those with OSA was significantly lower than in those without OSA (-1.99 ± 1.63 versus -1.27 ± 1.14 , $P=0.045$). In univariate analysis, body mass index, forced expiratory volume in 1 second, percentage of predicted value, incremental shuttle walk test, apnea-hypopnea index, and oxygen desaturation index (ODI) were significantly associated with BMD. After multivariate linear regression analysis, the ODI was still an independent factor for BMD. In addition, smaller total lung capacity is significantly associated with higher ODI and lower BMD, which implies that lower BMD might cause severer OSA via decreased total lung capacity.

Conclusion: OSA may be an independent factor for BMD in patients with COPD, which implies a possible vicious cycle takes place in these patients.

Keywords: chronic obstructive pulmonary disease, osteoporosis, total lung capacity

Introduction

Chronic obstructive pulmonary disease (COPD) is a serious health burden and a major cause of mortality worldwide.¹ Aside from the progressive loss of pulmonary function, extra-pulmonary comorbidities such as low skeletal muscle mass, cardiovascular disease, pulmonary hypertension, obstructive sleep apnea (OSA), and osteoporosis play an important role in the mortality of COPD patients.¹⁻⁴

Osteoporosis, characterized by a decrease in bone mineral density (BMD), is reported to affect 9%–69% of patients with COPD,⁵ indicating that COPD patients have a high risk of developing osteoporosis. The etiology of osteoporosis in COPD patients is complex and variable, and includes chronic systemic inflammation (TNF- α promoting bone loss),⁶ therapy (corticosteroid treatment), and natural changes because of aging, physical deconditioning (low skeletal muscle mass).⁷

With regard to physical activity, a recent study revealed that walking capacity is impaired when COPD patients have OSA, also called the overlap syndrome. In addition, this impairment can be partially reversed by continuous positive airway pressure

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(CPAP) treatment,⁸ implying that OSA is a possible cause for the low level of physical activity in COPD patients. Moreover, a low level of physical activity may lead to negative effects in patients with osteoporosis.⁹ Furthermore, OSA patients have been reported to have a higher avidity and cytotoxicity of $\gamma\delta$ T-cells, which are mainly attributed to the proinflammatory cytokine TNF- α .¹⁰ TNF- α promotes further bone loss,⁶ which may further contribute to osteoporosis. Therefore, OSA may be a possible etiology responsible for osteoporosis in COPD patients, a finding that has not previously been reported. The primary aim of this study was to evaluate the BMD between COPD patients with and without OSA. The secondary aim was to evaluate the association between BMD and severity of OSA.

Materials and methods

Study population

We retrospectively recruited patients with COPD from January 2008 to January 2013 in Chang Gung Memorial Hospital, a tertiary hospital in Taiwan. Patients were excluded if data of BMD and polysomnography were not available or if the patients had any history of malignancy. Those COPD patients would be referred to sleep laboratory while they had snoring. Therefore, data of polysomnography were not available if those COPD patients had no snoring history. The Chang Gung Medical Foundation Institutional Review Board approved this study (102-3093B) and waived the requirement for informed consent due to the retrospective nature of the study.

Study design

The medical records of each patient were reviewed to collect the clinical characteristics and laboratory results. In addition, data on BMD, polysomnography, pulmonary function, incremental shuttle walk test (ISWT), and medication were analyzed.

Definitions

COPD was defined as forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio less than 70% and an increase in forced expiratory volume in 1 second less than 12% of baseline after inhalation of β_2 agonist.¹ Based on the polysomnography results, OSA was defined as an apnea-hypopnea index (AHI) >15 per hour, of which $\geq 50\%$ were obstructive. Sleep stages and arousals were scored according to the AASM criteria.¹¹ Established criteria were used to score respiratory events

such as hypopnea, obstructive apnea, central apnea, mixed-type apnea, and Cheyne–Stokes respiration.^{12,13} Apnea was defined as oronasal flow cessation for more than 10 seconds. Hypopnea was defined as a 50% reduction in oronasal flow for more than 10 seconds; or a 30% reduction followed, by arousal or more than 3% decrease in oxygen saturation.¹² The BMD was determined by dual-energy X-ray absorptiometry. The BMD was expressed as a T-score (standard deviations from a young, sex-specific reference mean BMD).¹⁴ ISWT was performed as in a previous study.¹⁵

Statistical analysis

Data were expressed as mean $\pm$ standard deviation or mean $\pm$ standard error of the mean. The Student's *t*-test was used for comparisons of continuous variables between those with and without OSA, while the Mann–Whitney test was used for non-normal distributions. Categorical variables were compared by chi-square or Fisher's exact tests. The Pearson product correlation coefficient was used to examine correlations between variables and the BMD. Multivariate linear regression analysis was used to determine the independent factors associated with the BMD. A *P*-value less than 0.05 was considered to be statistically significant. All analyses were performed using the SPSS software package version 13.0 (SPSS Inc., Chicago, IL, USA).

Results

Demographic and clinical characteristics of the patients

A total of 312 patients with COPD were identified between January 2008 and January 2013, 30 of whom were excluded due to the following reasons: 194 (62.2%) did not have polysomnography data; 45 (14.4%) had malignancy; and seven (2.2%) did not have data on dual-energy X-ray absorptiometry for BMD. The records of the remaining 66 patients were further reviewed, of whom 35 had OSA and 31 did not. The baseline demographic data and clinical characteristics of these patients are listed in Table 1. The mean ages of the COPD patients with and without OSA were similar (71.5 and 71.6 years, respectively). The BMD in those with OSA was significantly lower than that in those without OSA (-1.99 ± 1.63 versus -1.27 ± 1.14 , $P=0.045$). Other characteristics including smoking, pulmonary function, and medications (including inhaled corticosteroids, long-acting β_2 agonists, long-acting muscarinic antagonists,

Table 1 Patients characteristics

Characteristics	COPD without OSA (n=31)	COPD with OSA (n=35)	P-value
Age	71.6±8.5	71.5±8.6	0.951
Male, n (%)	29 (93.5)	33 (94.3)	0.348
BMI	23.8±3.4	24.9±4.3	0.958
Smoke, PKY	50.5±28.9	51.7±22.3	0.850
Pulmonary function test			
FEV ₁ /FVC	55.5±9.4	54.4±10.4	0.651
FEV ₁ (% predicted)	46.8±15.9	46.4±23.0	0.927
FVC (% predicted)	60.2±15.7	61.1±23.9	0.850
Incremental shuttle walk test, m	279.7±107.2	240.9±88.4	0.168
BMD			
T-score (lumbar spine L2–4)	-1.27±1.14	-1.99±1.63	0.045
Medication			
LABA, n (%)	29 (93.5)	32 (91.4)	0.999
ICS, n (%)	29 (93.5)	32 (91.4)	0.999
LAMA, n (%)	24 (77.4)	31 (88.6)	0.324
Theophyllines, n (%)	7 (22.6)	12 (34.3)	0.415
Oral corticosteroids, n (%)	11 (35.5)	7 (20)	0.178
PPI, n (%)	11 (35.5)	17 (48.6)	0.326

Note: Data are presented as mean ± standard deviation, or number (percentage).
Abbreviations: BMD, bone mineral density; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; FVC, forced volume capacity; ICS, Inhaled corticosteroids; LABA, long-acting β_2 agonist; LAMA, long-acting muscarinic antagonist; OSA, obstructive sleep apnea; PKY, pack years; PPI, proton pump inhibitor.

theophylline, oral corticosteroids, and proton pump inhibitors) were similar between the two groups. With regards to the polysomnographic results (Table 2), the mean AHI in those with OSA was 37.0±16.7/h of sleep, indicating that most of the patients had severe OSA, accompanied by greater

Table 2 Polysomnographic results

	COPD without OSA (n=31)	COPD with OSA (n=35)	P-value
Total sleep time (minutes)	277.4±71.8	254.8±70.5	0.206
Sleep efficiency (%)	67.8±13.5	64.2±14.9	0.316
AHI events per hour	8.6±3.9	37.0±16.7	<0.001
ODI events per hour	4.4±3.6	21.1±15.4	<0.001
Average SaO ₂ %	93.7±2.2	93.2±2.5	0.363
Lowest SaO ₂ %	87.6±4.2	80.7±8.5	<0.001
Wake % TST	25.6±13.7	28.5±13.4	0.407
N1 % TST	18.8±12.1	20.5±9.9	0.525
N2 % TST	32.9±14.0	36.5±12.1	0.273
N3 % TST	10.8±11.0	6.5±9.1	0.091
REM % TST	11.7±6.8	8.0±7.1	0.032

Note: Data are presented as mean ± standard deviation.
Abbreviations: AHI, apnea-hypopnea index; COPD, chronic obstructive pulmonary disease; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; REM, rapid eye movement; SaO₂, oxygen saturation; TST, total sleep time.

desaturation (lowest oxygen saturation 80.7%) and less rapid eye movement stage (8% of total sleep time).

Univariate and multivariate linear regression analysis for the variables associated with BMD

In univariate analysis, body mass index (BMI), FEV₁ %, ISWT, AHI, and oxygen desaturation index (ODI) (Figure 1) were significantly correlated with BMD at the lumbar spine (Table 3), while age and use of inhaled corticosteroids, oral corticosteroids, and proton pump inhibitors were not. The multivariate stepwise linear regression analysis was used to analyze the independent factors contributing to BMD (Table 4). The association between BMD and AHI is revealed in Figure 1. Although, BMI, FEV₁ %, ISWT, AHI, and ODI were chosen to be analyzed in multivariate stepwise linear regression, only BMI, FEV₁ %, and ODI were independent factors for BMD.

The association between total lung capacity, BMD, and ODI

Figure 2 reveals an association between total lung capacity and ODI ($P<0.01$, $R=0.327$, $N=66$). In addition, an association between total lung capacity and BMD is shown in Figure 3. ($P=0.025$, $R=0.314$, $N=66$)

Discussion

The results of this study demonstrated that the BMD was worse in those with OSA than in those without OSA. In multivariate analysis, ODI was still significantly associated

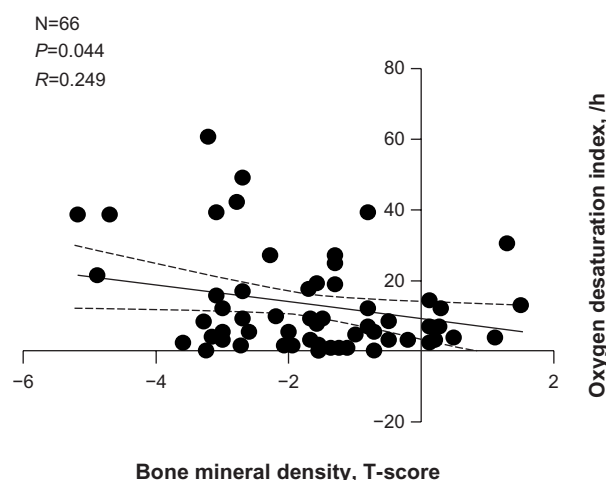


Figure 1 Correlation analysis: an association between bone mineral density and apnea-hypopnea index.

Table 3 Univariate analysis of variables associated with BMD at lumbar spine

Parameter	beta	Standard error	95% CI	P-value
Age	-0.013	0.021	-0.055 to 0.030	0.551
Sex	-0.290	0.761	-1.809 to 1.230	0.705
BMI	0.123	0.043	0.038 to 0.208	0.005
FEV ₁ %	0.025	0.009	0.008 to 0.043	0.005
ISWT, m	0.005	0.002	0.001 to 0.008	0.013
AHI	-0.021	0.009	-0.040 to -0.003	0.025
ODI	-0.026	0.013	-0.051 to -0.001	0.044
ICS	0.700	0.681	-0.661 to 2.061	0.308
Oral corticosteroids	-0.668	0.399	-1.466 to 0.130	0.099
PPI	-0.193	0.367	-0.926 to -0.540	0.600

Abbreviations: AHI, apnea-hypopnea index; BMD, bone mineral density; BMI, body mass index; CI, confidence interval; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; ISWT, incremental shuttle walk test; ODI, oxygen desaturation index; PPI, proton pump inhibitor.

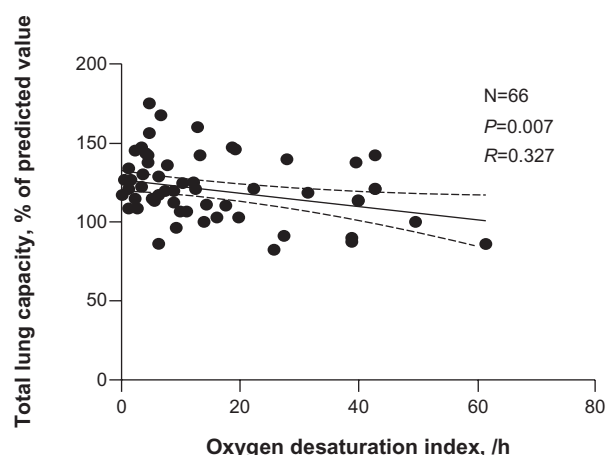
with BMD, which suggested that OSA played an important role in lower BMD in COPD patients. To the best of our knowledge, this finding has not previously been reported.

Osteoporosis is one of the systemic effects of COPD.¹ Moreover, osteoporosis is associated with the COPD mortality.¹⁶ However, the detailed mechanism by which osteoporosis develops in COPD patients is still under debate. It is likely that the pathogenesis is multifactorial and includes age, progressive reduction of physical activity, low BMI, disease severity (FEV₁ %), systemic use of corticosteroids, and systemic inflammation.^{5,17} Age was not associated with BMD in this study, which may be due to the small age span of the study population. The BMI and FEV₁ % were significantly associated with osteoporosis, which was compatible with previous reports.^{5,18,19} Interestingly, ODI as a cardinal feature of OSA was also an independent contributing factor to BMD, which may be explained by two possible reasons. One is the systemic inflammation and another one is reduced physical activity. It is known that systemic inflammation is aggravated in patients with OSA,²⁰ which is characterized by repetitive upper airway collapse and intermittent hypoxemia, and then it

Table 4 Multivariate linear regression: factors associated with BMD at lumbar spine

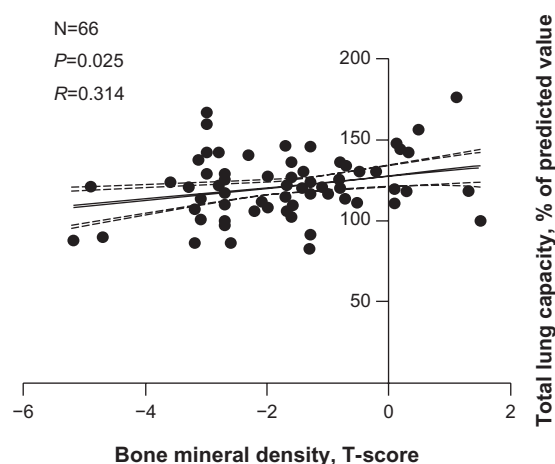
Parameter	beta	Standard error	95% CI	P-value
BMI	0.133	0.039	0.054 to 0.211	0.001
FEV ₁ %	0.022	0.008	0.006 to 0.038	0.008
ODI	-0.031	0.011	-0.054 to -0.009	0.007

Abbreviations: BMD, bone mineral density; BMI, body mass index; CI, confidence interval; FEV₁, forced expiratory volume in 1 second; ODI, oxygen desaturation index.

**Figure 2** Correlation analysis: an association between total lung capacity and oxygen desaturation index.

may affect the activity of osteoblasts and osteoclasts. Another possible reason is the reduced level of physical activity in COPD patients with OSA.⁸

With regards to systemic inflammation, increased concentrations of circulating inflammatory mediators such as TNF- α , IL-1, and IL-6 have been reported in COPD patients.^{21–23} Moreover, those oxidative stresses are associated with bone resorption during COPD exacerbation.²⁴ TNF- α stimulates osteoblastic cells to express RANKL and M-CSF, which in turn prompt macrophages to become osteoclasts, leading to bone resorption.^{25–28} In addition, TNF- α and IL-1, via activation of osteoclast surface receptors, potentiate osteoclastogenesis and bone resorption.²⁹ In addition, IL-6 is known to stimulate the formation of osteoclasts.^{29,30} OSA is accompanied by oxidative stress and inflammation via activation of NF- κ B and downstream pathway.¹⁰ Moreover, some evidence also revealed that

**Figure 3** Correlation analysis: an association between total lung capacity and bone mineral density.

TNF- α , IL-1, and IL-6 are significantly elevated in patients with OSA.^{10,31,32} In addition, hypoxia also induces the formation of giant osteoclasts.³³ Therefore, it is reasonable that the existence of OSA will lead to worsened BMD in COPD patients.

Physical activity is an important factor associated with osteoporosis. It has been reported to contribute to increased peak bone mass in youths,^{34,35} maintain bone mass in premenopausal women, and decrease loss of bone mass in postmenopausal women.³⁶ The benefits of physical activity in the prevention of osteoporosis have been revealed.^{37,38} Interestingly, a pronounced reduction in exercise capacity in COPD patients was observed in a previous study. In COPD patients who have OSA, the exercise capacity will be worse, although this can be restored with CPAP treatment.⁸ Therefore, this reduced level of physical activity may be another possible reason for the worse BMD in COPD patients with OSA.

Increases in lung volume have been documented to dilate the pharynx and decrease its collapsibility, which suggests that increases in lung volume will ameliorate the severity of OSA.^{39–41} In addition, the lower BMD is associated with lower total lung capacity in the present study. Similarly, a recent study revealed that COPD patients with osteoporosis are associated with deteriorated pulmonary function.⁴² In addition, while COPD patients with osteoporosis received vertebroplasty for the osteoporotic vertebral compression fractures, the pulmonary function can be improved after this procedure.⁴³ Decreases in lung volume in COPD patients with osteoporosis will deteriorate the severity of OSA. In addition, OSA will further deteriorate the osteoporosis in COPD patients. Therefore, while COPD patients have OSA, they will be in vicious cycle.

The major limitations of the present study are its retrospective nature, which may have led to bias in patient selection. Second, the sample size of the study is modest, and therefore the results of the study should be interpreted with caution. A prospective study with a larger sample size is warranted to further confirm the results. Physical activity has been reported as an independent factor associated with osteoporosis. However, ISWT was not an independent factor under multivariate analyses. The possible reason may be that ISWT is considered as a measurement of maximal exercise capacity, not a measurement of daily activity.⁴⁴ Therefore, the 6-minute walk test may be used to confirm if daily physical activity is an independent factor for osteoporosis in COPD patients with OSA in the further study. Finally, the population in this study was based in a sleep lab, so extrapolation of the results to the general population should be done with caution.

Conclusion

In conclusion, the BMD of COPD patients with OSA was significantly worse than that of COPD patients without OSA. Moreover, ODI was still an independent factor associated with BMD in multivariate analysis. In addition, smaller total lung capacity is significantly associated with higher ODI and lower BMD, which implies that lower BMD might cause severer OSA via decreased total lung capacity. Therefore, OSA may be a contributory factor to BMD in patients with COPD.

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Disclosure

The authors report no conflicts of interest in this work.

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